



## Clinical trial results:

**Etude multicentrique de phase III randomisée ouverte testant l'efficacité du gemtuzumab ozogamycin (MYLOTARG®) en association avec la chimiothérapie intensive chez les patients de 18 à 60 ans atteints de leucémie aiguë myéloblastique (LAM) avec cytogénétique intermédiaire.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2007-001209-64    |
| Trial protocol           | FR                |
| Global end of trial date | 26 September 2016 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 17 March 2019 |
| First version publication date | 17 March 2019 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | BRD 06/10-I |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00860639 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                      |
|------------------------------|------------------------------------------------------|
| Sponsor organisation name    | CHU Nantes                                           |
| Sponsor organisation address | 5 allée de l'Ile Gloriette, Nantes, France, 44093    |
| Public contact               | Pr MOREAU, CHU Nantes, philippe.moreau@chu-nantes.fr |
| Scientific contact           | Pr MOREAU, CHU Nantes, philippe.moreau@chu-nantes.fr |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 09 July 2012      |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 26 September 2016 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

Démontrer la supériorité de l'addition de gemtuzumab ozogamycin (Mylotarg®) à la chimiothérapie d'induction et de consolidation vs chimiothérapie seule en terme de survie sans évènement (event free survival : EFS) pour les patients âgés de 18 à 60 ans présentant une LAM avec cytogénétique intermédiaire non éligibles pour une allogreffe standard.

Protection of trial subjects:

Very close follow-up of the patients with biological analysis.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 26 October 2007 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 327 |
| Worldwide total number of subjects   | 327         |
| EEA total number of subjects         | 327         |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 327 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Intermediate acute leukaemia

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | First step              |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

Blinding implementation details:

Not applicable

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|           |       |
|-----------|-------|
| Arm title | Arm A |
|-----------|-------|

Arm description:

Induction course :

- Daunorubicin : 60 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m<sup>2</sup>/ day continuous infusion, D1, D2, D3, D4, D5, D6, D7
- Mylotarg® : 6 mg/m<sup>2</sup> via slow IV route for 2 hours on D4
- Premedication is required consisting of paracetamol 1g associated with an antihistamine :  
Dexchlorpheniramine 5 mg (Polaramine®) one hour before starting Mylotarg®
- Monitoring during infusion should include blood pressure and heart beat readings every 15 minutes for the first hour and subsequently every 30 minutes for 3 hours.

Consolidation course :

- Mitoxantrone : 12 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m<sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5
- Mylotarg® : 6 mg/ m<sup>2</sup> via slow IV route for 2 hours on D4

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Mylotarg              |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

6 mg/m<sup>2</sup> via slow IV route for 2 hours on D4

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Daunorubicin          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

60 mg / m<sup>2</sup>/ day slow IV for 15 minutes at D1, D2, D3

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Cytarabine            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

|                                                                                                                |                       |
|----------------------------------------------------------------------------------------------------------------|-----------------------|
| Dosage and administration details:                                                                             |                       |
| - Induction course : 200 mg / m <sup>2</sup> / day, continuous infusion at D1, D2, D3, D4, D5, D6, D7          |                       |
| - Consolidation course : 1 g / m <sup>2</sup> x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5      |                       |
| Investigational medicinal product name                                                                         | Mitoxantrone          |
| Investigational medicinal product code                                                                         |                       |
| Other name                                                                                                     |                       |
| Pharmaceutical forms                                                                                           | Solution for infusion |
| Routes of administration                                                                                       | Intravenous use       |
| Dosage and administration details:                                                                             |                       |
| 12 mg / m <sup>2</sup> / day slow IV for 15 minutes at D1, D2                                                  |                       |
| <b>Arm title</b>                                                                                               | Arm B                 |
| Arm description:                                                                                               |                       |
| Induction course :                                                                                             |                       |
| - Daunorubicin : 60 mg / m <sup>2</sup> / day, slow IV for 15 minutes, D1, D2, D3                              |                       |
| - Cytarabine : 200 mg / m <sup>2</sup> / day, continuous infusion, D1, D2, D3, D4, D5, D6, D7                  |                       |
| Consolidation course :                                                                                         |                       |
| - Mitoxantrone : 12 mg / m <sup>2</sup> / day, slow IV for 15 minutes, D1, D2                                  |                       |
| - Cytarabine : 1 g / m <sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5 |                       |
| Arm type                                                                                                       | Active comparator     |
| Investigational medicinal product name                                                                         | Daunorubicin          |
| Investigational medicinal product code                                                                         |                       |
| Other name                                                                                                     |                       |
| Pharmaceutical forms                                                                                           | Solution for infusion |
| Routes of administration                                                                                       | Intravenous use       |
| Dosage and administration details:                                                                             |                       |
| 60 mg / m <sup>2</sup> / day slow IV for 15 minutes at D1, D2, D3                                              |                       |
| Investigational medicinal product name                                                                         | Cytarabine            |
| Investigational medicinal product code                                                                         |                       |
| Other name                                                                                                     |                       |
| Pharmaceutical forms                                                                                           | Solution for infusion |
| Routes of administration                                                                                       | Intravenous use       |
| Dosage and administration details:                                                                             |                       |
| - Induction course : 200 mg / m <sup>2</sup> / day, continuous infusion at D1, D2, D3, D4, D5, D6, D7          |                       |
| - Consolidation course : 1 g / m <sup>2</sup> x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5      |                       |
| Investigational medicinal product name                                                                         | Mitoxantrone          |
| Investigational medicinal product code                                                                         |                       |
| Other name                                                                                                     |                       |
| Pharmaceutical forms                                                                                           | Solution for infusion |
| Routes of administration                                                                                       | Intravenous use       |
| Dosage and administration details:                                                                             |                       |
| 12 mg / m <sup>2</sup> / day slow IV for 15 minutes at D1, D2                                                  |                       |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Arm A | Arm B |
|-----------------------------------------------------|-------|-------|
| Started                                             | 119   | 119   |
| Completed                                           | 55    | 57    |
| Not completed                                       | 64    | 62    |
| Premature discontinuation                           | 64    | 62    |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The difference is due to the fact that the study has 2 periods.

## Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Second step                 |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

Blinding implementation details:

Not applicable.

## Arms

|           |       |
|-----------|-------|
| Arm title | Arm B |
|-----------|-------|

Arm description:

Induction course :

- Daunorubicin : 60 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m<sup>2</sup>/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :

- Mitoxantrone : 12 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m<sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Daunorubicin          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

60 mg / m<sup>2</sup>/ day slow IV for 15 minutes at D1, D2, D3

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Mitoxantrone          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

12 mg / m<sup>2</sup>/ day slow IV for 15 minutes at D1, D2

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Cytarabine            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

- Induction course : 200 mg / m<sup>2</sup>/ day, continuous infusion at D1, D2, D3, D4, D5, D6, D7
- Consolidation course : 1 g / m<sup>2</sup> x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5

| Number of subjects in period<br>2 <sup>[2]</sup> | Arm B |
|--------------------------------------------------|-------|
|                                                  |       |
| Started                                          | 73    |
| Completed                                        | 73    |

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Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The difference is due to the fact that the study has 2 periods.

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | First step |
|-----------------------|------------|

Reporting group description: -

| Reporting group values                                | First step | Total |  |
|-------------------------------------------------------|------------|-------|--|
| Number of subjects                                    | 238        | 238   |  |
| Age categorical                                       |            |       |  |
| Units: Subjects                                       |            |       |  |
| In utero                                              | 0          | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0          | 0     |  |
| Newborns (0-27 days)                                  | 0          | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0          | 0     |  |
| Children (2-11 years)                                 | 0          | 0     |  |
| Adolescents (12-17 years)                             | 0          | 0     |  |
| Adults (18-64 years)                                  | 238        | 238   |  |
| From 65-84 years                                      | 0          | 0     |  |
| 85 years and over                                     | 0          | 0     |  |
| Gender categorical                                    |            |       |  |
| Units: Subjects                                       |            |       |  |
| Female                                                | 108        | 108   |  |
| Male                                                  | 130        | 130   |  |

## End points

### End points reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Induction course :

- Daunorubicin : 60 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m<sup>2</sup>/ day continuous infusion, D1, D2, D3, D4, D5, D6, D7
- Mylotarg® : 6 mg/m<sup>2</sup> via slow IV route for 2 hours on D4
- Premedication is required consisting of paracetamol 1g associated with an antihistamine : Dexchlorpheniramine 5 mg (Polaramine®) one hour before starting Mylotarg®
- Monitoring during infusion should include blood pressure and heart beat readings every 15 minutes for the first hour and subsequently every 30 minutes for 3 hours.

Consolidation course :

- Mitoxantrone : 12 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m<sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5
- Mylotarg® : 6 mg/ m<sup>2</sup> via slow IV route for 2 hours on D4

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Induction course :

- Daunorubicin : 60 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m<sup>2</sup>/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :

- Mitoxantrone : 12 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m<sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Induction course :

- Daunorubicin : 60 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m<sup>2</sup>/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :

- Mitoxantrone : 12 mg / m<sup>2</sup>/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m<sup>2</sup> x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

### Primary: Event-free survival

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Event-free survival <sup>[1]</sup> |
|-----------------|------------------------------------|

End point description:

Demonstrate the superiority of adding gemtuzumab ozogamycin (Mylotarg®) to induction and consolidation chemotherapy vs chemotherapy alone in terms of event-free survival (EFS) for patients from 18 to 60 years of age presenting AML with intermediate cytogenetics not eligible for a standard allograft.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the premature discontinuation of the study, it was impossible to perform the statistical analyses planned in the protocol.



| <b>End point values</b>          | Arm A              | Arm B              |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 119 <sup>[2]</sup> | 119 <sup>[3]</sup> |  |  |
| Units: Not applicable            |                    |                    |  |  |
| number (confidence interval 95%) | 45 (38 to 53)      | 45 (38 to 53)      |  |  |

Notes:

[2] - EFS at 3 years on overall population.

[3] - EFS at 3 years on overall population.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the signature of the consent form until the end of follow-up for the non-serious adverse events and until resolution for the serious adverse events.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Arm B - First and second step |
|-----------------------|-------------------------------|

Reporting group description: -

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events                                              | Arm B - First and second step | Arm A              |  |
|---------------------------------------------------------------------|-------------------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                               |                    |  |
| subjects affected / exposed                                         | 149 / 192 (77.60%)            | 113 / 119 (94.96%) |  |
| number of deaths (all causes)                                       | 91                            | 56                 |  |
| number of deaths resulting from adverse events                      |                               |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |                    |  |
| Neoplasms benign and malignant                                      |                               |                    |  |
| subjects affected / exposed                                         | 10 / 192 (5.21%)              | 9 / 119 (7.56%)    |  |
| occurrences causally related to treatment / all                     | 3 / 10                        | 1 / 9              |  |
| deaths causally related to treatment / all                          | 2 / 8                         | 1 / 8              |  |
| Vascular disorders                                                  |                               |                    |  |
| Vascular disorder                                                   |                               |                    |  |
| subjects affected / exposed                                         | 11 / 192 (5.73%)              | 11 / 119 (9.24%)   |  |
| occurrences causally related to treatment / all                     | 5 / 12                        | 3 / 13             |  |
| deaths causally related to treatment / all                          | 1 / 1                         | 0 / 0              |  |
| Surgical and medical procedures                                     |                               |                    |  |
| Lung lobectomy                                                      |                               |                    |  |
| subjects affected / exposed                                         | 1 / 192 (0.52%)               | 0 / 119 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1                         | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0              |  |
| General disorders and administration site conditions                |                               |                    |  |

|                                                     |                   |                   |  |
|-----------------------------------------------------|-------------------|-------------------|--|
| General disorder and administration site conditions |                   |                   |  |
| subjects affected / exposed                         | 24 / 192 (12.50%) | 24 / 119 (20.17%) |  |
| occurrences causally related to treatment / all     | 9 / 35            | 3 / 29            |  |
| deaths causally related to treatment / all          | 1 / 1             | 1 / 1             |  |
| Immune system disorders                             |                   |                   |  |
| Immune system disorder                              |                   |                   |  |
| subjects affected / exposed                         | 10 / 192 (5.21%)  | 11 / 119 (9.24%)  |  |
| occurrences causally related to treatment / all     | 0 / 13            | 1 / 14            |  |
| deaths causally related to treatment / all          | 0 / 1             | 0 / 1             |  |
| Reproductive system and breast disorders            |                   |                   |  |
| Reproductive system and breast disorder             |                   |                   |  |
| subjects affected / exposed                         | 0 / 192 (0.00%)   | 2 / 119 (1.68%)   |  |
| occurrences causally related to treatment / all     | 0 / 0             | 2 / 3             |  |
| deaths causally related to treatment / all          | 0 / 0             | 0 / 0             |  |
| Respiratory, thoracic and mediastinal disorders     |                   |                   |  |
| Respiratory, thoracic and mediastinal disorder      |                   |                   |  |
| subjects affected / exposed                         | 26 / 192 (13.54%) | 10 / 119 (8.40%)  |  |
| occurrences causally related to treatment / all     | 8 / 33            | 5 / 12            |  |
| deaths causally related to treatment / all          | 2 / 4             | 0 / 0             |  |
| Psychiatric disorders                               |                   |                   |  |
| Psychiatric disorder                                |                   |                   |  |
| subjects affected / exposed                         | 1 / 192 (0.52%)   | 0 / 119 (0.00%)   |  |
| occurrences causally related to treatment / all     | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all          | 0 / 0             | 0 / 0             |  |
| Investigations                                      |                   |                   |  |
| Investigation                                       |                   |                   |  |
| subjects affected / exposed                         | 5 / 192 (2.60%)   | 2 / 119 (1.68%)   |  |
| occurrences causally related to treatment / all     | 2 / 5             | 1 / 2             |  |
| deaths causally related to treatment / all          | 0 / 0             | 0 / 0             |  |
| Injury, poisoning and procedural complications      |                   |                   |  |
| Poisoning deliberate                                |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 192 (0.52%)   | 0 / 119 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac disorders                               |                   |                   |  |
| Cardiac disorder                                |                   |                   |  |
| subjects affected / exposed                     | 10 / 192 (5.21%)  | 5 / 119 (4.20%)   |  |
| occurrences causally related to treatment / all | 2 / 11            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Nervous system disorders                        |                   |                   |  |
| Nervous system disorder                         |                   |                   |  |
| subjects affected / exposed                     | 15 / 192 (7.81%)  | 13 / 119 (10.92%) |  |
| occurrences causally related to treatment / all | 4 / 25            | 6 / 17            |  |
| deaths causally related to treatment / all      | 1 / 3             | 1 / 1             |  |
| Blood and lymphatic system disorders            |                   |                   |  |
| Blood and lymphatic system disorders            |                   |                   |  |
| subjects affected / exposed                     | 98 / 192 (51.04%) | 86 / 119 (72.27%) |  |
| occurrences causally related to treatment / all | 195 / 269         | 160 / 240         |  |
| deaths causally related to treatment / all      | 0 / 0             | 1 / 1             |  |
| Eye disorders                                   |                   |                   |  |
| Eye disorder                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 192 (0.00%)   | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal disorders                      |                   |                   |  |
| Gastrointestinal disorder                       |                   |                   |  |
| subjects affected / exposed                     | 14 / 192 (7.29%)  | 12 / 119 (10.08%) |  |
| occurrences causally related to treatment / all | 3 / 16            | 3 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hepatobiliary disorders                         |                   |                   |  |
| Hepatobiliary disorder                          |                   |                   |  |
| subjects affected / exposed                     | 11 / 192 (5.73%)  | 22 / 119 (18.49%) |  |
| occurrences causally related to treatment / all | 6 / 12            | 16 / 30           |  |
| deaths causally related to treatment / all      | 1 / 1             | 3 / 3             |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Rash macular                                    |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 192 (0.52%)   | 0 / 119 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal and urinary disorders                     |                   |                   |  |
| Renal and urinary disorder                      |                   |                   |  |
| subjects affected / exposed                     | 7 / 192 (3.65%)   | 3 / 119 (2.52%)   |  |
| occurrences causally related to treatment / all | 1 / 7             | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Musculoskeletal and connective tissue disorder  |                   |                   |  |
| subjects affected / exposed                     | 3 / 192 (1.56%)   | 4 / 119 (3.36%)   |  |
| occurrences causally related to treatment / all | 0 / 4             | 1 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Infections and infestations                     |                   |                   |  |
| Infections and infestations                     |                   |                   |  |
| subjects affected / exposed                     | 63 / 192 (32.81%) | 58 / 119 (48.74%) |  |
| occurrences causally related to treatment / all | 33 / 85           | 39 / 94           |  |
| deaths causally related to treatment / all      | 2 / 6             | 2 / 5             |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Metabolism and nutrition disorder               |                   |                   |  |
| subjects affected / exposed                     | 8 / 192 (4.17%)   | 3 / 119 (2.52%)   |  |
| occurrences causally related to treatment / all | 2 / 8             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Arm B - First and second step | Arm A           |  |
|-------------------------------------------------------|-------------------------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                               |                 |  |
| subjects affected / exposed                           | 1 / 192 (0.52%)               | 0 / 119 (0.00%) |  |
| Ear and labyrinth disorders                           |                               |                 |  |
| Hypacusis                                             |                               |                 |  |
| subjects affected / exposed                           | 1 / 192 (0.52%)               | 0 / 119 (0.00%) |  |
| occurrences (all)                                     | 1                             | 0               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22 February 2008 | <ul style="list-style-type: none"><li>- Modification of typos on protocol and annexes</li><li>- Updating of listing of investigators</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 04 March 2009    | Updating of listing of investigators : addition of 4 news centers, and 5 news centers realizing graft only                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 08 November 2010 | <ul style="list-style-type: none"><li>- Changing the protocol will have more than one treatment arm (arm without Mylotarg®)</li><li>- Continuation of the ancillary study (resumption of inclusions)</li><li>- Changing the timing of samples of residual disease (abandonment of post transplant points) and adding a molecular marker.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 16 November 2011 | <ul style="list-style-type: none"><li>- Resumption of inclusions : temporary stop in april 2009, following DMSC opinion who wanted more analysis about safety. Indeed, after the first intermediary analysis (100 patients), one stop criteria seemed to be reached (rate of death in Mylotarg arm), the DMSC requested a new analysis on the 175 patients included at the time, and a stop of inclusion pending result. After this second analysis, none stop criteria was reached.</li><li>- Precision on treatment diagram :<ul style="list-style-type: none"><li>. SCT advisable in case of RCI after first consolidation</li><li>. SCT regardless of molecular status for blastic patients at J15, and patient with central nervous disorders at diagnose</li></ul></li><li>- Modifications in SAE collection for hematological reaction : only unexpected was collected (than 60 days for induction course, and 45 days for consolidations course).</li><li>- - Updating of listing of investigators.</li></ul> |
| 05 July 2012     | <ul style="list-style-type: none"><li>- Updating of listing of investigators</li><li>- Extension of the inclusions period</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 06 February 2013 | Premature stop inclusions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 07 February 2014 | <ul style="list-style-type: none"><li>- Updating of listing of investigators (change of principal investigator in Poitiers)</li><li>- Modification of term monitoring patients</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 14 April 2014    | <ul style="list-style-type: none"><li>- Updating of listing of investigators (change of principal investigator in Colmar)</li><li>- Modification of expected SAE post graf collection</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption                                                                                                                                                                                                                                                                                                                                                                                                      | Restart date     |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 10 April 2009 | Temporary stop in april 2009, following DMSC opinion who wanted more analysis about safety. Indeed, after the first intermediary analysis (100 patients), one stop criteria seemed to be reached (rate of death in Mylotarg arm), the DMSC requested a new analysis on the 175 patients included at the time, and a stop of inclusion pending result. After this second analysis, none stop criteria was reached. | 15 December 2009 |

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Notes:

## **Limitations and caveats**

None reported

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## **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/25008258>

<http://www.ncbi.nlm.nih.gov/pubmed/24557850>